



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,180	07/11/2001	Keith D. Allen	R-477	1187

7590 06/19/2002
DELTAGEN, INC.
1003 Hamilton Avenue
Menlo Park, CA 94025

EXAMINER

PAPPU, SITA S

ART UNIT	PAPER NUMBER
----------	--------------

1636

DATE MAILED: 06/19/2002 //

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/904,180

Applicant(s)

ALLEN, KEITH D.

Examiner

Sita Pappu

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 May 2002.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) 16 and 27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 and 17-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Currently, claims 1-27 are pending in the instant application. This Office Action is in response to the communication filed by the Applicant in paper #10 on 05/06/2002.

Election/Restrictions

Applicant's election, with traverse, of Group I, claims 1-15, 17-26, is acknowledged. Applicant traversed on the grounds that the Inventions of Groups II and III are related to the Invention of Group I and that a search can be performed without a serious burden to the examiner. However, the Applicant does not offer any support for this assertion. Applicant's arguments are fully considered, but are not found persuasive. The agent of Group II and the data stored in a database of Group III are distinct from the targeting construct, the KO mouse and the methods of making the KO mouse and using the KO mouse in a method of identifying an agent having an effect on a phenotype, because a search for the agent of Group II would not reveal art on the transgenic animal and the data in the database. Similarly, a search for the data in the database would not reveal art on the agent of Group II or the targeting construct and the methods of using the transgenic animal of Group I. Thus, the searches are not coextensive.

Thus, the original restriction is still deemed proper and is therefore, made FINAL.

Accordingly, claims 16 and 27 are withdrawn from consideration. This paper contains an examination of claims 1-15, 17-26 on their merits.

Priority

Applicant's claim of priority to the provisional applications 60/217,329 (filed 07/11/2000), 60/262,126 (filed 01/16/2001), and 60/300,896 (filed 06/26/2001) is acknowledged.

Drawings

Draftsperson objected to the drawings. See attached PTO-948. Applicant is required to submit the drawing corrections within the time period set in this Office Action. See 37 C.F.R. 1.85(a). Failure to take corrective action within the set time period will result in ABANDONMENT OF THE APPLICATION.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-15, 17-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous knockout mouse comprising a disruption in the stefin homolog gene comprising the sequence set forth in SEQ ID NO:1 and exhibiting phenotypic features such as hyperactivity, decreased propensity to despair, schizophrenic behavior and decreased prepulse inhibition as compared to wild type mice, a method of producing such a transgenic mouse, and a method of identifying an agent that modulates the expression and/or function of stefin homolog gene comprising the sequence set forth in SEQ ID NO:1 and thereby ameliorates a phenotype associated with the disruption, and a cell derived from the KO mouse, does

not reasonably provide enablement for any transgenic and/or knockout animal comprising any disruption in any stefin homolog gene. Further, the specification is not enabling for a knockout mouse comprising any disruption in any stefin homolog gene and for any cell comprising any disruption in a stefin homolog gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 5-15, 17-26 are drawn to a cell comprising a disruption in a stefin homolog gene, a non-human transgenic animal comprising a disruption in a stefin homolog gene, a cell from that transgenic animal, a method of producing the mouse with any disruption in the said gene, and a method of identifying an agent having an effect on a phenotype associated with the transgenic mouse. Thus, the nature of the

invention is directed to transgenic animals and methods of using the transgenic animals in identifying agents that modulate gene expression.

Breadth of Claims:

In the instant case, the claims 5-15, 17-26 encompass any transgenic animal containing any disrupted allele for the gene that encodes any stefin homolog. Further, the claims encompass any knockout mouse comprising any disruption in stefin homolog gene and exhibiting the phenotypes of hyperactivity, decreased propensity to despair, and schizophrenic behavior as compared to wild type mice. Further, the claims encompass any cell comprising any disruption in a stefin homolog gene and encompass all cells capable of undergoing homologous recombination (specification page 3, line 5). The disruption, as disclosed in the specification (page 7, line 6) includes any insertion, deletion or substitution in any portion of the gene (introns, exons, regulatory regions). The claims, therefore, encompass all such disruptions and also cover animals that exhibit enhanced stefin homolog activity (page 7, lines 15-23).

The specification does not provide an enabling disclosure for the full scope of transgenic animals of the type claimed. The only embodiment enabled by the specification within the scope of claims 5-15, 17-26 is for a homozygous knockout mouse comprising a disruption in the stefin homolog gene comprising the set forth in SEQ ID NO:1, that results in loss of function of the stefin homolog and exhibiting phenotypic features such as hyperactivity, decreased propensity to despair, schizophrenic behavior and decreased prepulse inhibition as compared to wild type mice, a method of producing such a transgenic mouse, and a method of identifying an

agent that modulates the expression of stefin homolog gene and thereby ameliorates a phenotype associated with the disruption. Thus the breadth of claims is very broad and encompasses any transgenic animal and a knockout mouse with any disruption in any stefin homolog gene and includes any and all mutant forms, substitutions, deletions, or insertions in any stefin homolog gene (specification, page 7, lines 15-23).

Amount of guidance in the specification and Working Examples:

The specification discloses the use of a specific stefin homolog gene as set forth in SEQ ID NO:1 in producing a homozygous transgenic, knockout mouse and using the homozygous KO mouse to screen for agents that modulate its expression and/or function through the use of known screening methods wherein the knockout mouse exhibits phenotypic changes that include hyperactivity, decreased propensity to despair, schizophrenic behavior or decreased pre-pulse inhibition as compared to wild type mice.

The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that encodes a murine stefin homolog gene of SEQ ID NO:1 wherein the disruption results in loss of function of the stefin protease. The specification does not teach how to make and use the invention with other species of transgenic or knockout animals and with any knockout mouse with any form of disruption in the gene encoding any stefin protease, as claimed in the claims 5-15, 17-26. Further, the specification does not teach how to make and use any cell comprising

any type of disruption in a stefin homolog gene as claimed. The scope of claims 5-15, 17-26 thus surpasses that enabled by the specification.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention with any and all transgenic animals as claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that encodes a murine stefin homolog wherein the gene knocked out is a nonfunctional stefin protease inhibitor gene of SEQ ID NO:1. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all transgenic animals and/or transgenic mice carrying any and all transgene(s) of the types recited in the claims.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous stefin protease inhibitor gene knockout mouse comprising a disruption in the stefin protease inhibitor gene comprising the sequence set forth in SEQ ID NO:1 and fails to disclose the phenotypes of any and all KO animals with a

disruption in any stefin homolog gene. Thus, the phenotype of any transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals, including mice, that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. Thus, the specification is enabling for a method of identifying an agent that modulates the phenotype of a KO mouse using only a homozygous KO mouse of the instant invention.

Further, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). Thus, the invention while being enabled for a homozygous knockout mouse containing two disrupted alleles for the gene comprising the sequence set forth in SEQ ID NO:1 and encodes a stefin protease inhibitor, does not extend the predictability of the invention to other animal systems.

The particular genetic elements required for expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, the phenotype of knockout animals is not always predictable. For example, Jacks et al. (1992) describe Rb KO mice that do not display retinoblastoma; rather they exhibit the unexpected phenotype of pituitary tumors. The pituitary tumors arise from cells lacking a wild-type Rb allele. Thus, tumors were found to arise not in retinas, as in humans, but in the pituitary gland (page 299, Discussion, paragraphs 1 and 3). Therefore, in the

absence of specific guidance and working examples, the production of transgenic animals with the scope as claimed is unpredictable. In such a situation, one skilled in the art would not know how to make and use the invention as claimed, without undue experimentation.

The specification fails to provide an enabling disclosure for the preparation of other species of knockout animals besides mice having a disruption in the stefin protease inhibitor gene because the guidance offered in the specification is limited to the preparation of mice harboring such mutations and no teachings or guidance are offered in regard to how one would have prepared any other type of animal having the recited gene disruption. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out the method. The only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. S38, column 1, paragraph 1.

Thus, knockout animals cannot be prepared for any species other than the mouse.

Since ES cell technology was required to produce the claimed animals and practice the claimed methods of using such animals, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals and to practice of the claimed methods in species other than mice.

In view of the limited guidance in the specification, and limited working examples directed to transgenic, knockout mice with a specific knockout gene and exhibiting a specific phenotype, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to make and use the invention in its full scope as claimed. Thus, the enabled scope of the claims is limited to a homozygous knockout mouse comprising a disruption in the stefin protease inhibitor gene as set forth in SEQ ID NO:1 and exhibiting phenotypic features such as hyperactivity, decreased propensity to despair, schizophrenic behavior or decreased pre-pulse inhibition as compared to wild type mice, a method of producing such a transgenic mouse, and a method of identifying an agent that modulates the expression and/or function of stefin protease inhibitor gene and thereby ameliorates a specific phenotype associated with the said disruption.

Claims 1-15, 17-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention. Applicants are referred to the guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, No. 4, pp. 1099-1111 (also available at www.uspto.gov).

The specification does not provide or point to a written description of the genus of stefin homolog genes recited in the claims. Claims 1-15 are directed to a transgenic and/or knockout animal and a cell containing any disruption in any stefin homolog gene. However, the specification only describes a single species of a transgenic, knockout mouse of the type claimed, wherein the said disruption is within the gene that encodes a specific stefin, a murine stefin homolog gene comprising the SEQ ID No:1. The specification fails to teach other "stefin homolog genes" from other species of animals besides mice. In analyzing whether a written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the claims encompass the whole genus of 'stefin homolog genes' and include any and all transgenic animals that contain any altered allele for the gene that encodes a stefin. Thus for the claims to meet the written description requirement, other representative species of "stefin homolog genes", should be described by their complete structure or by other relevant identifying characteristics, in the specification.

Next, then, it is determined if a representative number of species have been sufficiently described by other relevant identifying characteristics. In the instant case, no identifying characteristics are provided for the genus of stefin homolog gene disruptions recited in the claims. Thus the limited information in the specification is not

Art Unit: 1636

deemed sufficient to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed genus of stefin homolog gene disruptions. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus of "stefin homolog genes".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 and 14, 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 14 are indefinite in their recitation of "the function of a stefin homolog gene". The meaning of this phrase is not clear and as such the metes and bounds of the phrase are not clearly set forth. Clarification is required. Claim 15 is rejected insofar as it depends from claim 14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15, 17-26, are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsui et al. (1993, *Genomics* Vol. 15, no. 3, pp. 507-514) and Pennachio et al. (1998, *Nature Genetics*, vol. 20, no.3, pp. 251-258) further in view of Capecchi et al. (1989, *TIG*, vol. 5, no. 3, pp. 70-76).

Tsui et al. teach the nucleotide sequence of the murine stefin homolog genes (Fig. 3, page 509).

Tsui et al. do not teach the use of their polynucleotide sequence to generate KO mice or targeting constructs.

Pennachio et al. (1996) teach KO mice deficient in cystatin B, a cysteine protease inhibitor belonging to the stefin family of protease inhibitors (page 251, abstract) and teach that such KO mice develop neurological disorders (page 255, subsection "Discussion") and advocate that the creation of knockout mice deficient in this gene, should elucidate their precise role and biological function. Pennachio et al. thus teach that mice knockout for cystatin genes are a good model to study the function of stefin homolog genes (page 257, left column, concluding sentence) and thereby provide the motivation to generate knockout mice having a disruption in a stefin

Art Unit: 1636

homolog gene. Methods of generating mice deficient in a gene are known in the art at the time of filing, as taught by Capecchi et al. (1989, TIG, vol. 5, no. 3, pp. 70-76).

Therefore it would have been obvious to one of ordinary skill in the art to use the nucleotide sequence of Tsui et al. to generate knockout mice and use them as model systems to screen for agents that modulate the function, and expression of stefin homolog genes, with a reasonable expectation of success. The motivation to do so was provided by Pennachio et al. and the expectation of success was derived from the teachings of Capecchi et al. (1989) who taught that KO mice can be successfully generated by gene targeting techniques and from Pennachio et al. who taught that cystatin deficient mice can be generated successfully using knockout techniques.

Claims 1-15, 17-26, are rejected under 35 U.S.C. 103(a) as being unpatentable over Sasaki et al. (1998, Genomics Vol. 49, no. 2, pp. 167-179) and Pennachio et al. (1998, Nature Genetics, vol. 20, no.3, pp. 251-258) further in view of Capecchi et al. (1989, TIG, vol. 5, no. 3, pp. 70-76).

Sasaki et al. teach the nucleotide sequence of the murine blastocyst cystatin B cDNA (Table 2, page 172; GenBank Accession number C89521) that is identical to SEQ ID NO:1 of the instant invention.

Sasaki et al. do not teach the use of their polynucleotide sequence to generate KO mice or targeting constructs.

Pennachio et al. (1996) teach KO mice deficient in cystatin B, a cysteine protease inhibitor belonging to the stefin family of protease inhibitors (page 251,

Art Unit: 1636

abstract) and teach that such KO mice develop neurological disorders (page 255, subsection "Discussion") and advocate that the creation of knockout mice deficient in this gene, should elucidate their precise role and biological function. Pennachio et al. thus teach that mice knockout for cystatin genes are a good model to study the function of stefin homolog genes (page 257, left column, concluding sentence) and thereby provide the motivation to generate knockout mice having a disruption in a stefin homolog gene. Methods of generating mice deficient in a gene are known in the art at the time of filing, as taught by Capecchi et al. (1989, TIG, vol. 5, no. 3, pp. 70-76).

Therefore it would have been obvious to one of ordinary skill in the art to use the nucleotide sequence of Sasaki et al. to generate knockout mice and use them as model systems to screen for agents that modulate the function, and expression of stefin homolog genes, with a reasonable expectation of success. The motivation to do so was provided by Pennachio et al. and the expectation of success was derived from the teachings of Capecchi et al. (1989) who taught that KO mice can be successfully generated by gene targeting techniques and from Pennachio et al. who taught that cystatin deficient mice can be generated successfully using knockout techniques.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305 1998. The fax phone numbers for the organization where this application is assigned are (703) 308 4242 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Tracey Johnson at (703) 305-2982.

S. Pappu
June 17, 2002



**JAMES KETTER
PRIMARY EXAMINER**